REMARKS

Reconsideration is respectfully requested. Claims 88-138 are pending. Claims 1-87, 93, and 118 have been cancelled. Claims 110 and 113-117, 119-121, and 122-134 are withdrawn as being drawn to a non-elected group, but certain of these claims have been amended in anticipation of possible rejoinder. Claims 88-92, 94, 96-98, 103, 108-117, 119, 122, 123, 128, and 131-134 have been amended. Claims 135-138 have been added. Thus, Claims 88-92, 94-109, 111, 112 are currently under review. No new matter has been added due to the amendments. Support for the amendments is found in the original claims. There is no change in inventorship based on the amendments.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

In addition, applicants reserve the right to rejoinder of restricted claims under MPEP §821.04.

Examiner Interview

Applicant would like to thank the Examiner for the time spent discussing this case on February 7, 2008. During the interview it was agreed that this application would focus on 239 substitutions in this application.

Restriction Requirement

Applicants have withdrawn Claims 110 and 113-117, 119-121, and 122-134 as being drawn to a non-elected group, but certain of these claims have been amended in anticipation of possible rejoinder. The Examiner has confirmed that Claims 113-117, 119-121, and 122-134 drawn to methods fall under the original restriction in the present case, dated April 21, 2006, which recited 2 groups (compositions and methods).

Applicants believe that claims 90-92, 94-102 fall within the species election and believe that these claims should not be withdrawn.

Applicants believe that 239D has been found to be free to prior art, therefore the prior art search should be extended. Applicants note that the claims are now directed to antibodies and immunoadhesins that comprise specifically recited amino acid substitutions at position 239, namely D, E, Q and T. That is, the Applicants have withdrawn all claims directed to the other 17 amino acid positions of the claims and have limited the substitutions to 4 specifically identified amino acid substitutions, of which substitution D has already been searched. Thus, the burden on the Examiner to examine additional species as species are found allowable has been significantly reduced. Applicants request that the Examiner search 239E as the next variant to be searched.

Priority

Applicants respectfully traverse this observation of the Examiner. The Applicants respectfully draw the Examiner's attention to Figures 2, 10 and 11 of USSN 60/414,433, which clearly shows a variety of variant amino acids at position 239. For example, Figure 2 shows **239E** and **239R** at row 4 of the first table, and **239D**, **239E, 239K** and **239R** at row 5 of the second table. The legend of Figure 2 and the text of the application show these variants are for increased binding to FcγR. At a minimum, the Examiner should acknowledge the priority for 239D and 239E.

Moreover, the legend of Figure 10 discloses that: "For each chain A Fc region listed all amino acids except proline and cysteine were substituted separately." The Legend of Figure 11 discloses that "For each chain A Fc region listed all amino acids except proline and cysteine were substituted separately." Thus USSN 60/414,433 discloses all substitutions except proline and cysteine of the 239 position. Thus, in fact, 17 out of 19 species (e.g. all substitutions except wild type and proline and cysteine) are disclosed in USSN 60/414,433. Applicants submit that this fully supports the genus of variants at position 239.

The Examiner states that Figures 10 and 11 are not relevant as they show variants that abrogate binding. However, as stated in the legends for both figures, "[m]utations with negative energies in both the presence and absence of receptor and mutations with positive energies in both the presence and absence of receptor are not shown". Thus these Figures call out only 4 variants that abrogate binding.

In addition, the Applicants respectfully point out the fact pattern of U.S. Patent No. 7,371,826, recently issued by the Examiner on Fc variants. In this case, as extensively outlined in the file history, the specification discloses a single species of variant, 434A, with increased binding to FcRn. The Examiner found this disclosure sufficient to enable the genus of all variants at position 434 that result in increased binding to FcRn. The Applicants respectfully request similar treatment.

Applicants are not claiming positions Pro (P) or Cys (C). Nor are the claims reciting substitutions N, F,H, Y or A. Therefore the Examiner's statements regarding these substitutions are not relevant to the claims.

Accordingly, the Applicants respectfully request an acknowledgement of such priority.

Rejections under 35 U.S.C. §112, first paragraph (enablement and written description)

Claims 88, 108, 109, 111 and 112 are rejected under 35 U.S.C. §112, first paragraph for lacking enablement and adequate written description.

The Examiner states in Section 9 that the antibody or immunoadhesin comprising an Fc region wherein the Fc region comprises a amino acid in position 239 wherein the substitution is not N, F, H, Y, or A. Applicant does not recite any of these specific substitutions in the rejected claims. Applicants respectfully submit that these claims are enabled and that there is adequate written description for the 239 variants recited, and therefore these rejection have been overcome.

Examiner has requested the deletion of the expression "a parent Fc polypeptide". In order to expedite prosecution, Applicant has deleted the expression. Examiner has requested the deletion of the expression "an antibody fragment" in claim 109. In order to expedite prosecution, Applicant has deleted the expression from this claim.

Therefore, Applicants respectfully submit that the claims are enabled and the rejection of the claims has been overcome.

Rejection under 35 U.S.C. §102(e)

Claims 88, 108, 109, 111 and 112 stand rejected over Presta (US 6,737,056) "*Presta*".

Anticipation requires that every limitation of the claim in issue be disclosed, either expressly or inherently, in a single prior art reference. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); M.P.E.P. § 2131 (citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). *Presta* fails to anticipate the claimed invention for the reasons stated below.

Presta's disclosure of position 239 and the separate teaching that amino acids can be substituted do not anticipate the specifically recited species of 239, namely D, E, Q and T and in some claims N, F, H and Y. Applicants respectfully submit that the recent Board of Patent Appeal and Interferences' decision in Ex parte Watkins (Appeal 2007-2523) is particularly relevant here since this rejection involves a similar fact pattern.

In *Watkins,* the Examiner relied on *Presta* to reject claim 1 and claims dependent therefrom of under 35 U.S.C. §102(e) as being anticipated. Specifically, the Board rejected the Examiner's reliance on *Presta's* definition of amino acid substitution which lists twenty standard amino acids, because such definition "does not describe substituting the amino acid at position 280 with any of these twenty amino acids." *Watkins* at 6. Moreover, the Board states:

> [W]e do not agree that Presta provides a specific teaching of substituting the amino acid at position 280 with each of these twenty amino acids and therefore with the three amino acids recited in claim 1. *Id.* at 6.

In the instant Office Action, the Examiner bases the rejection on the disclosures of *Presta* that is similar to the disclosure of *Presta* relied upon by the Examiner in *Watkins*, and relied on the similar reading of Ex parte A.

Pages 14-15 of *Presta* lists all of the twenty naturally occurred amino acids as potential substitutions, the same definition of "amino acid substitution" disclosed in *Presta* in *Watkins.* Thus, identical to *Watkins*, such definition "does not describe substituting the amino acid at position [293] with any of these twenty amino acids."

Therefore, *Presta* does not anticipate the claims. Applicants respectfully request that this ground for rejection be withdrawn and that the additional non-elected species be examined consistent with the election of species requirement.

The antibodies or immunoadhesins of claims 88, 108, 109, 111 and 112 comprise an antibody or immunoadhesin that has both a structural and functional limitation. Specifically, the

antibody or immunoadhesin a) includes at least one substitution at the position 239 – 4 substitutions are specifically identified in these claims, and b) "increases binding affinity to an FcγR as compared to [the] parent Fc polypeptide." Examiner has already stated that there is enablement and adequate written description to support the claims recitation of these 239 variants.

Presta does not teach the claimed species position 239 with or without the required functional limitation. At page 5, line 32, Presta discloses that a group of modifications that include elected position 239 display "reduced binding to an FcγR." At page 6, line 10, Presta discloses that a group of modifications that include position 239 display "reduced binding to an FcγRIIIa." The best demonstration of this is in Table 6, which discloses the sole substitution at position 239, which was an alanine substitution, 239A. Table 6 shows that 239A has reduced binding affinity to both FcγRIII and FcγRII. Amino acid substitutions that do not result in an Fc variant with increased binding affinity to an FcγR are outside the scope of the claims. Without meeting the positive functional limitation, Presta cannot anticipate the claim.

The claimed antibody or immunoadhesin is also not inherent in the teaching of Presta. To be inherent, the claimed limitation must "necessarily flow" from the teachings of the cited reference. The mere fact that a claimed compound may have the claimed function is insufficient to establish inherent anticipation. See M.P.E.P. § 2163.07(a). As noted above, page 5, line 32 of *Presta* discloses that modifications at position 239 display "reduced binding to an FcγR," page 6, line 10 of *Presta* discloses that modifications at position 239 display "reduced binding to an FcγRIIIa", and Table 6 shows the sole 239 variant, 239A, has decreased binding to both FcγRIII and FcγRII. One of skill in the art would not draw the conclusion that variants at position 239 would "necessarily" result in increased binding; rather, if anything, the opposite inference could be drawn.

Further, *Presta* does not disclose any specific substitution at position 239 that inherently has the claimed functional limitation. As discussed below, *Presta* provides a generalized teaching for making modifications at a large genus of numerous positions in the Fc region. In this context, such a generalized teaching of a genus is not an anticipatory teaching of a specific substitution at a specific position. As such, *Presta* does not teach any substitution at the elected position 239 that inherently "increases binding affinity to an FcγR" as claimed.

Presta does not anticipate the claims for the reasons described above in the response to the rejection under 35 U.S.C. §102(b). First, *Presta* neither expressly nor inherently teaches an antibody or immunoadhesin of a parent Fc polypeptide comprising "an amino acid substitution at 239D, 239E, 239Q, or 239T, wherein said antibody or immunoadhesin increases binding affinity to an FcγR as compared to said Fc polypeptide." Second, *Presta II* fails to anticipate the elected substitution species 239D, as well as substitutions E, Q or T.

The Examiner states that the arguments regarding the 239D substitution are considered moot since the claims that are drawn to 239D are not rejected. The claims do specifically recited 239D, 239E, 239Q, and 239T, therefore this rejection is moot.

As such, the presently claimed invention is not anticipated by *Presta*. Applicants respectfully request that this ground for rejection be withdrawn.

Rejection under 35 U.S.C. §103(a)

Claims 88, 89, 103-106, 108, 109, 111, and 112 stand rejected under *Presta*.

Applicant confirms that the subject matter of the claims was commonly owned at the time any inventions covered therein were made.

Presta has been discussed above. It is again noted that Presta does not teach any substitutions at position 239 that enhance binding to an FcγR. Moreover, Presta only teaches one substitution in the specification – an alanine. But for the Examiner error in allowing claim 13 in Presta to include position 239 which has absolutely no support in the specification for enhancing binding, this rejection would be moot. The only teaching in Presta is that an alanine substitution at position 239 decreases binding to an Fc FcγR. With respect to 239 and claim 13, Presta is not an enabling reference. Nor is there adequate (any) written description to support a claim for enhanced binding at position 239.

One skilled in the art would not be led to substitute D, E, Q or T for the existing Alanine because it decreases binding to an FcγR.

The Examiner refers to col. 12 to support the position that amino acid substitutions are interchangeable. The Examiner's position was rejected in the Watkins case. While the basis of the rejection was 102(e) in Watkins, the point made is identical. As stated above, the Board rejected the Examiner's reliance on *Presta's* definition of amino acid substitution which lists twenty standard amino acids, because such definition "does not describe substituting the amino

acid at position 280 with any of these twenty amino acids." *Watkins* at 6. Moreover, the Board states:

> [W]e do not agree that Presta provides a specific teaching of substituting the amino acid at position 280 with each of these twenty amino acids and therefore with the three amino acids recited in claim 1. *Id.* at 6.

Applicant believes that the Board would take the same position with respect to this rejection.

Further, Applicant notes that Alanine is described as hydrophobic. None of the specifically recited substitutions claimed by Applicant are hydrophobic. Therefore one skilled in the art would not be taught to substitute a variant claimed by Applicant. Presta states that the elected substitution is acidic. The 20 amino acids have very different chemical characteristics and cannot be simply substituted one for another.

The Examiner has repeatedly noted in the instant Office Action that various substitutions have different effects, and notes the unpredictability of the art (see, for example, Section 9, last paragraph). The Examiner cannot on one hand say that the prior art shows unpredictability for the purposes of enablement and simultaneously argue that the prior art is predictable for the purposes of a §103 rejection.

Following the analysis outlined in the M.P.E.P. §2143 and the teachings of the Supreme Court in the KSR case (*KSR v. Telefax*, 82 USPQ2d 1385 (2007)), the teachings of Presta do not render the claimed invention obvious:

A) combining prior art elements according to known methods to yield predictable results.

As has been asserted by the Examiner substituting one amino acid for another is unpredictable. Moreover, since there is NO teaching of enhanced binding at position 239 in the specification, one skilled in the art would not be able to combine elements to produce the result recited in the claims.

B) Simple substitution of one known element for another to obtain predictable results

The Examiner refers to col. 12 to support the position that amino acid substitutions are interchangeable. The Examiner's position was rejected in the Watkins case. While the basis of the rejection was 102(e) in Watkins, the point made is identical. As stated above, the Board rejected the Examiner's reliance on *Presta's* definition of amino acid substitution which lists

twenty standard amino acids, because such definition "does not describe substituting the amino acid at position 280 with any of these twenty amino acids." *Watkins* at 6. Moreover, the Board states:

> [W]e do not agree that Presta provides a specific teaching of substituting the amino acid at position 280 with each of these twenty amino acids and therefore with the three amino acids recited in claim 1. *Id.* at 6.

Applicant believes that the Board would take the same position with respect to this rejection.

Further, Applicant notes that Alanine is described as hydrophobic. None of the specifically recited substitutions claimed by Applicant are hydrophobic. Therefore one skilled in the art would not be taught to substitute a variant claimed by Applicant. The teachings in Presta either teach away from the substitution of D (or any of the other amino acids) or alternatively in no way suggest it based on the very different chemical characteristics of naturally occurring S or substituted A.

D) Applying a known technique to a known product ready for improvement to yield predictable results

The comments with respect to item A are equally applicable here. While one skilled in the art is "capable" of performing tests, there has to be a teaching or motivation or suggestion to try certain substitutions. There are none in Presta as Presta does not teach any enhanced variants at position 239.

E) Obvious to try.

The comments above are equally applicable here. There is no teaching or motivation to try the substitutions claimed by Applicant because there is only one variant (alanine) and that variant DOES NOT enhance binding at position 239. The Examiner states that "a person of ordinary skill in the art has good reason to pursue the known options". However, as required by the KSR Guidelines issued by the Office, the Examiner is required to identify those good reasons. The Examiner does not do so here, nor are there any such reasons.

F) Some teachings, suggestion or motivation in the prior art that would have lead one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

As previously stated, there is no teaching motivation or suggestion in Presta to support this argument. There is no teaching in Presta that would lead one skilled in the art to identify variants at position 239 that enhance binding to the specifically recited substitutions. This is required by KSR and by the KSR guidelines. Again Col. 12 provides no teaching that D would be a good substitution based on the disclosure that A does not enhance binding. There is no teaching there, just a list of 20 amino acids. One skilled in the art is not guided by a list without any suggestions.

Even with the lack of suggestion in Presta one skilled in the art could not have known that D would be a substitution to enhance binding. The only teaching in Presta is that alanine decreases binding. There is no basis for enhanced binding here.

Conclusion

In light of the above amendments and remarks, Applicants believe that this case is now in condition for allowance. Early notification is respectfully requested. Should there be any remaining issues that remain unresolved, the Examiner is encouraged to telephone the undersigned.

Please direct further questions in connection with this Application to the undersigned at (415) 442-1000.

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Dated: 8/4/08 RMS

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Filed 37 C.F.R. §1.34

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